

## Clinical Significance of Serum Procalcitonin in Patients with Community-acquired Lobar Pneumonia

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**Background:** Community-acquired pneumonia (CAP) is a common respiratory disorder in children, which necessitates hospitalization. Bacterial pneumonia, especially lobar pneumonia and parapneumonic effusions, is associated with considerably severe clinical course and extensive alveolar infiltrates. Serum procalcitonin (PCT) level has been used to distinguish bacterial from viral infections, but its usefulness is disputed. The diagnostic accuracy and usefulness of PCT, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell (WBC) count were determined by comparing their values in the patients with CAP with those in healthy controls.

**Methods:** The serum PCT levels, as well as CRP level, ESR, and WBC counts, were measured in 76 hospitalized patients with CAP (lobar pneumonia, 16; bronchopneumonia, 60) and 18 healthy controls. Serum PCT level was measured using VIDAS<sup>®</sup> BRAHMS PCT (Biomérieux, France), and ROC curve analysis was performed to evaluate its diagnostic accuracy.

**Results:** Serum PCT levels were higher in the patients with CAP than in healthy controls, especially in the patients with lobar pneumonia than in those with bronchopneumonia. Serum CRP level was also significantly elevated in the patients with CAP, especially in those with lobar pneumonia. The diagnostic accuracy of serum PCT level for the diagnosis of lobar pneumonia was better than those of serum CRP level and ESR. The serum PCT level was significantly correlated with the CRP level, ESR, and WBC count.

**Conclusions:** Serum PCT level was a better marker than CRP level or ESR for the diagnosis of lobar pneumonia in children with CAP. (*Korean J Lab Med 2010;30:406-13*)

**Key Words :** Procalcitonin, Child, C-reactive protein, Pneumonia, Erythrocyte sedimentation rate

### INTRODUCTION

Community-acquired pneumonia (CAP) is one of the most common respiratory disorders in children, which necessitates frequent hospitalization [1]. CAP is often diagnosed on the basis of chest radiological findings of

consolidation or infiltration. Both viral and bacterial pathogens can cause CAP. Bacterial pneumonia cannot be completely differentiated from viral pneumonia on the basis of clinical or chest radiographic findings.

Procalcitonin (PCT), a precursor of the hormone calcitonin, is produced in the medullary C-cells of the thyroid gland and is associated with calcium metabolism [2, 3]. PCT is produced in the parenchymal cells in response to microbial toxins or inflammatory mediators such as interleukin (IL)-1 $\beta$  and tumor necrosis factor (TNF)- $\alpha$  [4]. The level of PCT in healthy individuals is less than 0.1 ng/mL [5] and remains low in individuals with viral and non-infectious diseases [6].

Previous studies have provided inconsistent results

Received : February 15, 2010  
Revision received : July 24, 2010  
Accepted : July 27, 2010

Manuscript No : KJLM10-033

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ISSN 1598-6535 ©The Korean Society for Laboratory Medicine

regarding the clinical value of PCT. PCT has been reported to have no association with the severity and cause of CAP and plays no role in the diagnosis of bacterial CAP [7]; however, it is a useful marker for differentiating bacterial CAP from viral pneumonia in hospitalized children [8, 9].

Nonspecific inflammatory markers such as C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and white blood cell (WBC) count have been widely used to distinguish severe bacterial infections from viral infections. CRP is known to be a better predictor of serious bacterial infection than WBC count [10]. However, some studies have reported that CRP level has limited value because of its low sensitivity and specificity for bacterial infection [10, 11].

Early detection of bacterial infection can reduce the need of unnecessary antibiotic therapy. However, isolation of microbes is slightly difficult in children with CAP due to the difficulties in sputum expectoration and low positive rate of blood culture [12]. One of the indicators of bacterial pneumonia is chest radiographic findings. Lobar pneumonia or parapneumonic effusion is suggestive of bacterial infection, whereas bronchopneumonia is more frequent in viral pneumonia cases than in bacterial pneumonia cases [13]. We evaluated the serum levels of PCT in children with CAP according to the radiographic findings and compared the results with those for other inflammatory markers to assess the diagnostic value of PCT level in children with lobar pneumonia.

## MATERIALS AND METHODS

### 1. Study groups

Between January 2008 and May 2009, 76 children with CAP (36 boys and 40 girls; aged 3–158 months; mean age, 39 months) and 18 afebrile healthy children were prospectively recruited for this study. The children with CAP had acute respiratory symptoms with fever (temperature  $\geq 38.0^{\circ}\text{C}$ ) and showed new infiltrates on their chest radiographs. The exclusion criteria for the study were as fol-

lows: presence of malignancy, immunodeficiency, or congestive heart disease; presence of an alternative diagnosis during the follow-up; or hospitalization during the preceding 72 hr. Parapneumonic effusions were detected by chest radiography. Patients were excluded from the study if the cause of illness was identified as a pathological condition other than pneumonia, or if the pleural fluid was a transudate.

Of the 76 patients with CAP, 24 (32%) were less than 24 months old, 28 (36%) were between 2 and 5 yr of age, and 24 (32%) were older than 5 yr of age. Patients were classified as having bronchopneumonia (N=60) or lobar pneumonia (focal or segmental consolidations were considered to be indicative of lobar pneumonia; N=16). A pediatrician and pediatric radiologist independently reviewed and classified chest radiographic findings. All the patients who were less than 2 yr old had bronchopneumonia, 9 of the 28 patients (32%) between 2 and 5 yr of age had lobar pneumonia, and 7 of the 25 patients (28%) older than 5 yr of age had lobar pneumonia. Of the patients with lobar pneumonia, 5 had parapneumonic effusions. None of the patients with pneumonia died or were admitted to the intensive care unit during hospitalization.

Eighteen healthy children who visited our hospital for routine evaluations, with no fever or respiratory symptoms, were enrolled as the control group (9 boys and 9 girls; age range, 8–142 months; mean age, 53 months). The study design was approved by the ethics committee of our hospital, and informed consent was obtained from the parents of all the children recruited for this study.

### 2. Microbiological investigations

To identify the causative organisms, we performed blood and/or pleural fluid cultures, rapid urinary *Streptococcus pneumoniae* antigen assay, and evaluation for antibodies to *Mycoplasma pneumoniae* in the children with pneumonia. Blood cultures were performed in all the patients with CAP, and pleural fluid cultures were performed in 5 patients with parapneumonic effusions. None

of the bacterial cultures were positive for any pathogens. We did not perform cultures, PCRs, or serologic investigations for viruses.

Pleural fluid was obtained from patients with parapneumonic effusions by thoracentesis. The pleural fluid was assessed for biochemistry, WBC count, Gram staining, and aerobic and anaerobic bacterial culture. An exudate was defined as a ratio of protein in the pleural fluid to that in the serum of  $>0.5$ , and the ratio of lactate dehydrogenase in the pleural fluid to that in the serum of  $>0.6$ .

The urine samples of children with pneumonia were analyzed for the presence of *S. pneumoniae* cell-wall antigens using the rapid urine *S. pneumoniae* antigen assay kit (Binax NOW<sup>®</sup>, Portland, ME, USA). This test device contains an immunochromatographic membrane that can be used to detect soluble pneumococcal antigens in the human urine. The sensitivity and specificity of rapid urine *S. pneumoniae* antigen assay has been reported to be 77-92% and 97-100%, respectively [14]. *S. pneumoniae* infection was diagnosed when *S. pneumoniae* was identified in blood culture or when the rapid urine antigen assay yielded a positive result.

Blood samples were drawn on days 1 and 14 of treatment for the evaluation of antibodies to *M. pneumoniae* in the patients with pneumonia. *M. pneumoniae* infection was diagnosed when there was a 4-fold increase in the antibody titer during the 14 days of treatment.

### 3. Measurement of PCT level, CRP level, ESR, and WBC count

At the time of admission, venous blood was drawn from all the patients and control subjects and was centrifuged at  $1,000\times g$  for 10 min at 4°C. The samples were tested for PCT within 30 min after receipt of them at the clinical laboratory sampling. The serum level of PCT was measured by using an enzyme-linked fluorescence assay (VIDAS<sup>®</sup> BRAHMS PCT assay; Biomerieux, Lyon, France), according to the manufacturer's instructions; the detection limit of this assay is 0.05 ng/mL. The upper limit of reference interval used in this study was 0.5 ng/mL, as

suggested by the manufacturer, whereas the upper limits for elevated serum PCT level were 1.0 ng/mL, which has been suggested by Moulin et al. [8], and 2.0 ng/mL, which has been suggested by Toikka et al. [9] and Prat et al. [15].

The WBC count was determined by flow cytometry (Beckman coulter, Pasadena, CA, USA), according to the manufacturer's instructions. The ESR was determined using a quantitative capillary photometry method by using Test 1 (Alifax, Padova, Italy). The cut-off limits used were 30 mm/hr for ESR and  $15 (\times 10^3/\mu\text{L})$  for WBC count [7, 8, 16, 17]. The serum CRP levels were assayed using a highly sensitive immunonephelometric method by using a BNII nephelometer (Siemens, Marburg, Germany). The reference interval for serum CRP level was below 0.59 mg/L, and the cut-off limit for elevated CRP levels was 6 mg/L [8, 16, 17].

### 4. Statistical analysis

Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Data were reported as mean  $\pm$  SD. Results were analyzed using the t-test, Fisher's exact test, one-way ANOVA followed by the Dunnett's test, and Spearman correlation test. The area under ROC curves (AUROCs) of serum PCT and CRP levels and ESR for the diagnosis of lobar pneumonia were calculated. The diagnostic accuracy values of sensitivity (SN), specificity (SP), and likelihood ratio (LR) were calculated. The optimal cutoff value was set for the diagnosis of lobar pneumonia. A level of  $P < 0.05$  was considered as statistically significant.

## RESULTS

The PCT level in the patients with CAP ( $2.06 \pm 0.60$  ng/mL, mean  $\pm$  SD) was significantly higher than that in the healthy controls ( $0.05 \pm 0.02$  ng/mL). In patients with pneumonia, the serum PCT level was significantly higher in those more than 5 yr of age ( $4.14 \pm 1.41$  ng/mL) than in those younger than 2 yr of age ( $0.17 \pm 0.03$  ng/mL). The serum PCT level of 0.5 ng/mL was used to compare the

PCT levels between patients with CAP and healthy controls. Of the 76 patients with CAP, 53 (70%) had mean PCT levels of below 0.5 ng/mL, and 23 (30%) had serum PCT levels of above 0.5 ng/mL. All healthy controls had serum PCT levels of below 0.5 ng/mL. There was a significant difference in the serum PCT levels at a cutoff value of 0.5 ng/mL between the patient and control groups. The patients with CAP had significantly higher serum CRP levels and WBC counts than those in healthy controls (Table 1).

The levels of serum PCT, CRP, ESR, and WBC counts of the patients with lobar pneumonia were compared to those of the patients with bronchopneumonia (Table 2). Of the 76 patients, 60 had bronchopneumonia and 16 had lobar pneumonia. Of the 16 patients with lobar pneumonia, 5 had parapneumonic effusions. The serum PCT levels were significantly higher in the patients with lobar pneumonia than in those with bronchopneumonia (5.19 ± 0.74 ng/mL vs. 1.13 ± 0.53 ng/mL; *P*=0.04). Serum PCT levels of above 0.5 ng/mL were noted more frequently in patients with lobar pneumonia than in patients with bronchopneumonia (62% vs. 25%). There was no significant difference in the PCT level depending on whether parapneumonic effusions were present or not (data not shown). The serum CRP level and ESR were significantly higher in the patients with lobar pneumonia than in those with

**Table 1.** Serum levels of PCT and inflammatory markers in the entire study group

|                              | Patients with pneumonia (N=76) | Control (N=18) | <i>P</i> value     |
|------------------------------|--------------------------------|----------------|--------------------|
| Mean age (months)            | 39                             | 53             |                    |
| Number of males              | 36                             | 9              |                    |
| PCT (ng/mL)                  | 2.06 ± 0.60                    | 0.05 ± 0.02    | 0.002              |
| <2 yr old                    | 0.17 ± 0.03                    | -              |                    |
| 2-5 yr old                   | 4.14 ± 0.74                    | -              |                    |
| >5 yr old                    | 4.14 ± 1.41                    | -              | 0.01*              |
| CRP (mg/L)                   | 8.00 ± 0.75                    | 0.35 ± 0.00    | 0.01               |
| WBC ( × 10 <sup>3</sup> /μL) | 12.8 ± 0.6                     | 9.7 ± 0.6      | 0.01               |
| PCT level                    |                                |                |                    |
| <0.5 ng/mL, n (%)            | 53 (70)                        | 18 (100)       | 0.007 <sup>†</sup> |
| ≥0.5 ng/mL, n (%)            | 23 (30)                        | 0 (0)          |                    |

PCT and CRP levels and ESR values are expressed as the mean ± SD. \*One-way ANOVA, followed by Dunnett's test; <sup>†</sup>Fisher's exact test. Abbreviations: PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell.

bronchopneumonia. The WBC count was not significantly different between patients with lobar pneumonia and those with bronchopneumonia.

ROC curves obtained at the time of admission for the serum PCT levels in the patients with lobar pneumonia are shown in Fig. 1. The AUROC at the time of admission for the serum PCT levels (0.83; 95% confidence interval (CI), 0.65–0.99) was significantly higher (*P*<0.01) than those for the CRP level (0.77; 95% CI, 0.59–0.95) and

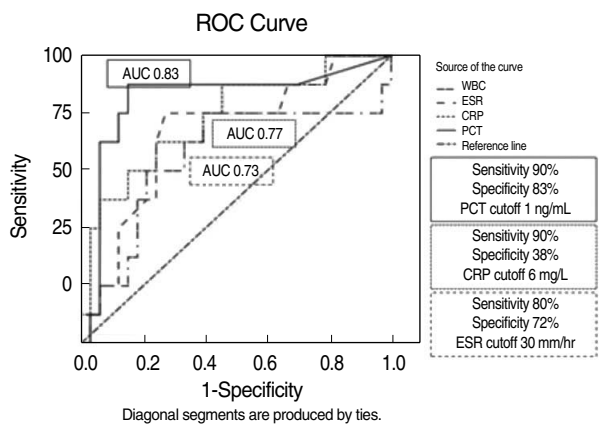
**Table 2.** Serum levels of PCT and inflammatory markers according to the types of pneumonia

|                              | Bronchopneumonia (N=60) | Lobar pneumonia (N=16) | <i>P</i> value |
|------------------------------|-------------------------|------------------------|----------------|
| PCT (ng/mL)                  | 1.13 ± 0.53             | 5.19 ± 0.74            | 0.04           |
| CRP (mg/L)                   | 6.7 ± 0.68              | 12.27 ± 2.17           | 0.03           |
| ESR (mm/h)                   | 21.2 ± 2.0              | 32.4 ± 3.8             | 0.04           |
| WBC ( × 10 <sup>3</sup> /μL) | 12.42 ± 0.62            | 14.59 ± 1.76           | 0.23           |
| PCT level                    |                         |                        |                |
| <0.5 ng/mL, n (%)            | 45 (75)                 | 6 (38)                 | 0.007*         |
| ≥0.5 ng/mL, n (%)            | 15 (25)                 | 10 (62)                |                |

PCT, CRP levels and ESR values are expressed as mean ± SD.

\*Fisher's exact test.

Abbreviations: PCT, procalcitonin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.



**Fig. 1.** ROC curves of serum PCT (AUC, 0.83; 95% CI, 0.65-0.99) and CRP (AUC, 0.77; 95% CI, 0.59-0.95) levels and ESR (AUC, 0.73; 95% CI, 0.54-0.92) for the diagnosis of lobar pneumonia in hospitalized children.

The area under the ROC (AUROC) for serum PCT was significantly higher than those of the CRP and ESR (*P*<0.01). The optimum diagnostic cutoff point for the serum PCT, CRP, ESR levels in this study was 1 ng/mL, 6 mg/L, 30 mm/hr by the ROC curve analysis.

Abbreviations: PCT, procalcitonin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; AUC, area under the curve.

**Table 3.** Diagnostic accuracies of serum PCT, CRP levels and ESR in the patients with lobar pneumonia

| Markers with cutoff values | SE (%) | SP (%) | LR+  | LR-  | DOR  |
|----------------------------|--------|--------|------|------|------|
| PCT>0.5 (ng/mL)            | 90     | 72     | 10.6 | 0.14 | 7.2  |
| PCT>1 (ng/mL)              | 90     | 83     | 11.4 | 0.12 | 8.4  |
| PCT>2 (ng/mL)              | 70     | 93     | 15.3 | 0.32 | 16.7 |
| CRP>6 (mg/L)               | 90     | 38     | 6.9  | 0.26 | 6.1  |
| ESR>30 (mm/hr)             | 80     | 72     | 6.8  | 0.28 | 7.3  |

Abbreviations: SE, sensitivity; SP, specificity; LR+, likelihood ratio of a positive result; LR-, likelihood ratio of a negative result; DOR, diagnostic odds ratio; PCT, procalcitonin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

ESR (0.73; 95% CI, 0.54-0.92). The AUROC for WBC count was not significantly different from that for the PCT level ( $P=0.19$ ). In this study, the optimum diagnostic cutoff point for serum PCT levels was 1 ng/mL, according to the ROC curve analysis. The sensitivity and specificity of the diagnostic accuracy of serum PCT levels for lobar pneumonia were 90% and 83%, respectively, at the cutoff of 1 ng/mL. The AUROC obtained at the time of admission for CRP level was 0.77 (95% CI, 0.59-0.95). The optimum diagnostic cutoff point for CRP level was 6 mg/L, according to the ROC curve analysis. The sensitivity and specificity of the diagnostic accuracy of CRP level for lobar pneumonia were 90% and 38%, respectively, at a cutoff of 6 mg/L. The optimum diagnostic cutoff point for ESR was 30 mm/hr, according to the ROC analysis. The sensitivity and specificity of the diagnostic accuracy of ESR for lobar pneumonia were 80% and 72%, respectively, at a cutoff of 30 mm/hr.

Comparison of the parameters, including serum PCT level, CRP level, and ESR, for the diagnostic accuracy for lobar pneumonia at different cutoff values is shown in Table 3. The results of this study showed that PCT had a maximum LR and odds ratio (OR) for the diagnosis of lobar pneumonia at a cutoff of 2 ng/mL. The LR and OR of PCT level for the diagnosis of lobar pneumonia were higher than those of the CRP level at a cutoff of 6 mg/L and those of ESR at a cutoff of 30 mm/hr. The diagnostic efficacy of acute inflammatory markers was compared between patients with mycoplasma pneumonia and those with streptococcal pneumonia. *M. pneu-*

*moniae* and *S. pneumoniae* were detected in 8 and 8 patients, respectively. None of the cultures were positive for *S. pneumoniae*. There were no significant differences in the levels of PCT and CRP, ESR, and WBC counts between the patients with mycoplasma infection and those with streptococcal infection (data not shown). Serum PCT levels showed significant correlations with CRP level, ESR, and WBC count (data not shown).

## DISCUSSION

The serum PCT levels in children with CAP were compared to those in healthy control subjects. The results showed that the serum PCT levels were elevated in children with pneumonia, especially in those with lobar pneumonia, compared to those with bronchopneumonia. This is the first report on a comparison of serum PCT levels between bronchopneumonia and lobar pneumonia in children.

In clinical practice, bacterial involvement is considered to be responsible for the appearance of alveolar infiltrates on chest radiographs; however, clinical studies have failed to confirm this finding [18-20]. There are no definitive findings on x-ray studies for differentiating bacterial pneumonia from viral pneumonia. However, unlike bronchopneumonia, lobar pneumonia or parapneumonic effusions are more often associated with a bacterial origin [13]. In a previous study, most children with lobar infiltrates had a bacterial infection, whereas interstitial infiltrates were noted in children with viral pneumonia and in those with bacterial pneumonia [21]. However, considering that lobar pneumonia is more likely to be associated with a bacterial origin, higher levels of PCT in the cases with lobar pneumonia compared to those with bronchopneumonia may be consistent with the elevated PCT levels in bacterial infections.

The PCT levels in lobar pneumonia may be higher because of the following reasons. A larger area of lung parenchyma is damaged by microorganisms in lobar pneumonia than in bronchopneumonia. Because the source of PCT is parenchymal cells, the amount of dam-

aged parenchymal area can be an important factor in determining the serum PCT level.

In this study, bacteria were not isolated from any of the blood cultures. This could be because of the lower sepsis rate in the cases with bacterial pneumonia or because the children underwent pretreatment with oral antibiotics before hospital admission. Isolation of bacterial pathogens is difficult in hospitalized children with CAP, because of the difficulty in sputum expectoration and low blood culture-positivity rate. Even with sepsis, the rate for the detection of bacteria in blood cultures is estimated to be less than 30%. PCR and cultures for the detection of viruses were not performed in this study. Therefore, the serum PCT levels that allow distinction of bacterial pneumonia from viral pneumonia could not be determined. Some studies have shown that PCT reduces the rate of antibiotic use in CAP and can be used as a therapeutic guideline for antibiotic therapy [22]. However, low levels of PCT cannot always rule out bacterial infection [23], and the level of PCT may be low in patients with sepsis [24]. Furthermore, even in virus-associated pneumonia, secondary bacterial infection can occur during treatment. Therefore, a complete clinical assessment, as well as assessment for other inflammatory markers, should be performed to determine the appropriate treatment approach.

In some studies, serum PCT values tended to be lower in less than 2-yr-old children than in older children [7, 16]. This is consistent with the results of our study. In this study, none of the less than 2-yr-old children had lobar pneumonia, whereas 28% of the more than 5-yr-old children showed lobar pneumonia. This could be because the rate of bacterial infection is higher in more than 5-yr-old children with CAP, whereas the rate of viral-associated pneumonia is higher in less than 2-yr-old children [13]. The highest frequency of viral pneumonia has been noted in children between 2 and 3 yr of age, and it decreases gradually thereafter [13]. Higher levels of PCT in older children may be due to the age-dependent difference in pneumonia occurrence.

In the present study, alveolar infiltrates were found to

be associated with elevated levels of CRP, PCT and ESR, but not with the WBC count. In previous studies, elevated CRP level and ESR, but not an elevated WBC count and PCT level, were found to be associated with alveolar infiltrates on chest x-rays [16, 17]. Another study reported that the PCT level was higher in alveolar pneumonia than in interstitial pneumonia [25]. However, no study has compared the serum PCT levels between patients with lobar pneumonia and those with bronchopneumonia.

In this study, the sensitivity and specificity of serum PCT level for the diagnosis of lobar pneumonia were found to be significantly higher than those of CRP level and ESR, although both the ESR and CRP values increased significantly in children with lobar pneumonia compared to those in children with bronchopneumonia. In this study, PCT level at a cutoff of 1 ng/mL had both the best sensitivity (90%) and specificity (83%) for the diagnosis of lobar pneumonia. This is in accordance with a previous study [8] that showed that the PCT level, at a threshold of 1 ng/mL, had greater positive and negative predictive values than those for CRP for the diagnosis of CAP in hospitalized children. In a recent study on adults with CAP, PCT level at a cutoff of 0.5 ng/mL was found to be more useful as a predictor than the CRP level [26].

The findings of this study showed a significant correlation between PCT and other inflammatory markers such as the WBC count, ESR, and CRP level, even though the PCT level was found to be a better predictor of lobar pneumonia than other inflammatory markers.

The following are the limitations of this study. No pathogen was identified in the blood cultures, and testing for viruses was not performed. Therefore, the use of the serum PCT level to differentiate bacterial from viral infections requires further confirmation. In addition, in order to determine the durations of high PCT levels in the serum, further study is required; serial measurements were not obtained in this study. The PCT levels were measured at time of admission; the onset of disease prior to admission differed across the patients. Therefore, the PCT level at the time of admission may not represent the peak PCT level in the patients. Furthermore,

the serum PCT levels could not be compared according to the severity of the disease, because the pneumonia severity index [27] was less than 2.

In conclusion, serum PCT level was found to be a better clinical marker than CRP level and ESR for the diagnosis of lobar pneumonia in children with CAP.

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